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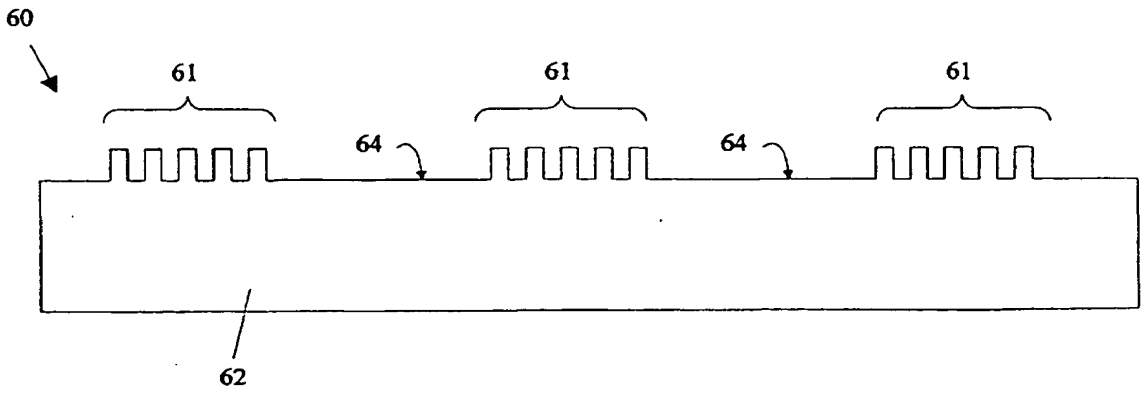

(57) Abstract

This invention is an apparatus (60) for disrupting a layer of skin having a known thickness without substantially disrupting underlying dermis layers below the layer of skin in question. The apparatus (60) includes a cutter having a plurality of micro-protrusions (61) having a height less than or equal to the thickness of the layer of skin, and a stop for preventing the apparatus (60) from penetrating said layer of skin beyond a predetermined distance. In the preferred embodiment of the present invention the micro-protrusions (61) comprise first and second groups of micro-protrusions (61) extending from a substrate, and the stop comprises a region of the substrate separating the first and second groups and recessed below the tops of the first and second groups of micro-protrusions (61). In one embodiment of the present invention, a means for moving the apparatus (60) relative to the layer of skin, is provided.

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MICROMECHANICAL DEVICE AND METHOD FOR ENHANCING DELIVERY OF COMPOUNDS THROUGH THE SKIN

Field of the Invention

The present invention relates to drug delivery systems, and more particularly, to a mechanical device that alters the outermost layer of skin for the improved delivery of compounds through the skin.

Background of the Invention

Transdermal delivery of medication is well known in the prior art. Transdermal patches are available for a number of drugs. Commercially available examples of transdermal patches include scopolamine for the prevention of motion sickness, nicotine for aid in smoking cessation, nitroglycerin for the treatment of coronary angina pain, and estrogen for hormonal replacement. Generally, these systems have drug reservoirs sandwiched between an impervious backing and a membrane face which controls the steady state rate of drug delivery. The systems usually are attached to the skin by an adhesive gel with the membrane face adjacent to the skin..

Transdermal medication has significant advantages over both hypodermic injection and oral administration. A transdermal patch can provide significantly greater effective blood levels of a beneficial drug because the drug is not delivered in spike concentrations as is the case with hypodermic injection and most oral administration. In addition, drugs administered via transdermal patches are not subjected to the harsh environment of the digestive tract. Hence, in principle, transdermal delivery provides a method for administrating drugs that would otherwise need to be administered via hypodermic injection or intravenous infusion because the drug is destroyed in the digestive tract or immediately absorbed by the liver. Conversely, the digestive tract and liver are not subjected to the drug in transdermal administration. Many drugs, such as aspirin, have an adverse effect on the digestive tract.

Prior art transdermal drug delivery systems may be divided into passive diffusion and active transport systems. Transdermal drug delivery by diffusion is by far the most common

of the transdermal methods. The nicotine patch is an example of this method of delivery (U.S. Patent #4,597,961 to Frank T. Etscorn). This process is based on presenting the medication in a high dose external to the dermis and allowing the chemical to diffuse into and through the skin. The degree of diffusion depends on the porosity of the skin, the size and polarity of the drug molecules, and the concentration gradient across the stratum corneum, the outermost layer of human skin. These factors generally limit this mode of delivery to a very small number of useful drugs with very small molecules or unique electrical characteristics.

Attempts to widen the range of drugs that may be transdermally delivered have led to the active methods mentioned above. The active diffusion systems involve iontophoresis, electroporation and ultrasound to increase the migration of the drug across the skin barrier. These methods attempt to electrically assist diffusion of the medication or apply high frequency electrical pulses or sound waves to the skin to improve absorption. Unfortunately, the high cost and inconvenience of providing portable electrical equipment have limited the commercial application of such active systems.

Accordingly, it is a general object of the present invention to provide an improved transdermal drug delivery system and method.

It is another object of the invention to eliminate or greatly reduce the pain of drug delivery by present skin-penetrating devices, such as needles, fluid jets, iontophoresis, etc.

It is another object of the present invention to provide a transdermal delivery system that does not rely on applied electric fields, yet allows drugs that could not previously be administered by passive diffusion to be so administered.

These and other objects of the present invention will become apparent to those skilled in the art from the following detailed description of the invention and the accompanying drawings.

Summary of the Invention

The present invention comprises an apparatus for mechanically disrupting a layer of skin having a known thickness without substantially disrupting underlying dermis layers below the layer of skin in question. The apparatus includes a cutter having a plurality of microprotrusions having a height less than or equal to the thickness of the layer of skin and a stop for preventing the apparatus from penetrating said layer of skin beyond a predetermined distance. In the preferred embodiment of the present invention, the microprotrusions comprise first and second groups of microprotrusions extending from a substrate, and the stop comprises a region of the substrate separating the first and second groups and recessed below the tops of the first and second groups of microprotrusions. In one embodiment of the present invention, a means for moving the apparatus relative to the layer of skin is provided. The motion pattern has an amplitude parallel to the surface of the skin that is less than the distance between the first and second groups of microprotrusions. The microprotrusions are preferably in the form of a bed of needles or cutting blades. The microprotrusions may be constructed in silicon or similar materials using conventional micro-machining techniques. Alternatively, the microprotrusions may be fabricated by molding plastics/polymers utilizing a micro-machined mold. After the layer of skin is mechanically disrupted, a drug or other chemical compound may be administered to the patient using conventional creams, ointments or transdermal patch techniques.

Brief Description of the Drawings

Figures 1-4 are cross-sectional views of a silicon substrate at various stages in the fabrication of a bed of microprotrusions according to the present invention.

Figure 5 is cross-sectional view of a mold and a bed of microprotrusions constructed thereon.

Figure 6 is a cross-sectional view of a micro-cutter according to the present invention.

Detailed Description of the Invention

The major limitation of current transcutaneous drug delivery systems is the inability or difficulty in diffusing the delivered drug through the stratum corneum, the outer approximate 10 μm of the skin over most of the body. The stratum corneum is a thin layer of dead skin cells that covers the epidermis and dermis layers of skin. Although only about 10 cells thick, the stratum corneum layer keeps water in the human body from evaporating through the skin. This critical role as a diffusion barrier for the prevention of water evaporation also serves to make the skin impermeable to the diffusion of most beneficial drugs from outside the body.

The present invention is based on mechanically penetrating or disrupting the stratum corneum layer, thereby improving the effectiveness of transdermal delivery of drugs incapable of diffusion through the stratum corneum. The simplest embodiment of the present invention comprises a bed of microneedles or microcutters that are just long enough to effectively penetrate the stratum corneum. This bed of microprotrusions can be placed on the skin and moved relative to it, either vertically and/or horizontally, in order to generate a large number of tiny micropenetrations and/or microdisruptions in the stratum corneum layer. This bed of microprotrusions can be inexpensively manufactured by one of several technologies commonly referred to as micro-machining (micro-mechanics, Micro Electro Mechanical Systems, known as MEMS, etc.).

The problems introduced by the stratum corneum have been recognized for some time. However, previous techniques for removal of the stratum corneum have introduced new problems which have prevented their commercial use. For example, techniques in which the stratum corneum is removed by placing sticky tape in contact with the skin and then ripping off the tape have been used. Unfortunately, such techniques are painful and, in addition, remove significant amount of underlying epidermis and dermis layers. The loss of the additional layers of skin can result in bleeding and the possibility of infection. Such techniques are impractical for clinical practice, and disrupt the skin such that healing takes a week or longer.

The present invention, however, utilizes a mechanical method for penetrating the stratum corneum layer without substantially damaging the underlying layers. Hence, blood

vessels and nerve endings are not damaged. The simplest embodiment of the present invention is a bed of microprotrusions that may be used as a stand-alone device to mechanically disrupt the stratum corneum layer. Such a device would be pressed to the skin to disturb the stratum corneum layer. The device is then removed and the drug applied using conventional creams, ointments, lotions or patch. The height of the microprotrusions is chosen to disrupt and penetrate the stratum corneum without significantly penetrating the underlying layers of skin which contain blood vessels and nerve endings that generate pain responses.

The manner in which such a bed of microprotrusions can be constructed is illustrated in Figures 1-5. Refer first to Figures 1-4 which illustrate one of several methods for the fabrication of a bed of microprotrusions in a silicon substrate 13. A layer 12 of silicon dioxide is first deposited on substrate 13. A layer 11 of photoresist is then deposited on oxide 12 and patterned using conventional photolithography techniques. The patterned photoresist layer is used to control the etching of the oxide layer using a fluorine reactive ion etch process which stops on the silicon. The patterned oxide layer is then used as a mask for a chlorine reactive ion etch that penetrates the silicon substrate leaving protrusions 16. The intermediate oxide masks ensure straight sidewalls and consistent edge depths. Alternatively, the microcutter may be composed of the structure shown in Figure 2 after the top layer of photoresist 11is removed, provided the silicon oxide layer 12 is deposited with a thickness approximately to the stratum corneum thickness.

Yet another alternative method for generating a microcutter comprising a bed of microprotrusions is illustrated in Figure 5 which is a cross-sectional view of a mold 24 used to fabricate, for example, a plastic/polymer microcutter 22. Plastic/polymer structures having features of the same general dimensions as those needed for the micro-cutter have been demonstrated in polystyrene. However, other plastics/polymers such as polycarbonate may be used. The mold may be constructed as described above. However, it will be apparent to those skilled in the art that a number of different methods for constructing a mold with the necessary microstructure may be utilized.

The resulting micro-cutters are sufficiently inexpensive to be disposable. Since the molding process involves temperatures in excess of those needed to provide sterilization, the resulting structures may be immediately packaged without further sterilization.

As noted above, the micro-cutter must be designed so as to disrupt the stratum corneum without interrupting the underlying layers of skin. To accomplish this, the micro-cutter must disrupt, remove or penetrate approximately the top 10 μm of skin and then stop. The preferred structure for accomplishing this is illustrated in Figure 6 which is a cross-sectional view of a micros cutter 60 according to the present invention. Micro cutter 60 comprises a large number of micro-cutter arrays 61 that are constructed on a substrate 62. The micro-cutter arrays are separated by smooth areas 64 that are recessed with respect to the top of the micro-cutter arrays. The depth of smooth areas 64 is set sufficiently large to allow improved drug delivery -- but sufficiently small to avoid pain or bleeding.

The micro-cutter may be attached to a vibrator or other mechanism for moving the micro-cutter with respect to the skin. If the pattern of movement of the micro-cutter is parallel to the surface of the skin, the motion parallel to the skin's surface ideally has an amplitude that is less than the distance between the individual micro-cutter arrays. These smooth unpatterned areas prevent the vibrating micro-cutter arrays from cutting any deeper than the height of the sub-arrays, because the smooth areas come to rest on nearby stratum corneum once the areas of stratum corneum under the micro-cutter arrays has been removed. The ratio of areas in the micro-cutter arrays and smooth areas must be such that the smooth areas arrest the skin-penetrating motion of the micro-cutter before the micro-cutters can penetrate the layers of skin significantly below the stratum corneum.

While the above described fabrication techniques utilized silicon substrates to form the microprotrusions directly or through molding of plastics/polymers, metals or the like, it will be apparent to those skilled in the art from the above discussion that microprotrusions may be fabricated as an inexpensive and identical array of microneedles by any one of several technologies known as micromachining, micromechanics, MEMS, etc. These microelectronic-like technologies typically first employ the deposition onto a substrate of various films on the size scale of the stratum corneum thickness. Examples of typical films

include silicon nitride, silicon oxide, polyimide, aluminum, gold, etc. Secondly, a photolithography technique imparts an image of an array of hundreds or thousands of tiny structures to the top film layer. After selective etching, this results in the fabrication of millions of identical microstructures on the size scale of the stratum corneum thickness. Other process steps include wet etching, plasma etching, or reactive ion etching a photosensitive polymer film (resist) on a silicon substrate or wafer as is common in the microelectronics industry. The films may be deposited by chemical vapor deposition techniques prior to the etching operation. The substrate is then bulk and/or surfaced micromachined to achieve the required height tolerance which is preferably $15 \pm 2\mu m$.

While the above described embodiments of the present invention utilized micro-cutter arrays that were composed of needle-like protrusions, it will be apparent to those skilled in the art that other shaped protrusions may also be utilized. For example, the protrusions may take the form of small blades having a height of approximately 10 to 20 μm and a length of 40 to 200 μm.. Blades have the advantage of being less likely to break during the movement of a micro-cutter relative to the patient's skin. The preferred direction of movement of such a micro-cutter is parallel to the length of the blade. In contrast, the micro-needles described above are preferably moved perpendicular to the patient's skin so as to puncture the stratum corneum.

While the above described embodiments of the present invention have utilized a micro-cutter that just penetrates the stratum corneum, other embodiments that penetrate deeper may also be used. The epidermis layer under the strattum corneum is approximately 100 μm thick, and like the stratum corneum, has no blood vessels or nerve endings. The epidermis, however, does have live cells that are fed by diffusion from the dermis below. Hence, the micro-cutter can penetrate to a depth of the epidermal/dermal interface without encountering the problems of prior art devices that attempt to disrupt the skin barrier -- but damage the dermis layer as well.

Various modifications to the present invention will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Accordingly, the present invention is to be limited solely by the scope of the following claims.

WHAT IS CLAIMED:

1. An apparatus[60] for disrupting a layer of skin, said layer of skin having a known thickness, said disruption being accomplished without substantially disrupting underlying dermis layers below said layer of skin, said apparatus[60] comprising: cutting means comprising a plurality of microprotrusions[61] having a height less than or equal to said thickness of said layer of skin; and stop means[64] for preventing said apparatus[60] from penetrating said layer of skin beyond a predetermined distance.

2. The apparatus[60] of Claim 1 wherein said microprotrusions[61] comprise first and second groups of microprotrusions[61] extending from a substrate and wherein said stop means comprises a region[64] of said substrate separating said first and second groups.

3. The apparatus[60] of Claim 1 further comprising means for moving said apparatus[60] relative to said layer of skin in a motion pattern having an amplitude parallel to the layer of skin that is less than the distance between said first and second groups of microprotrusions[61] .

4. The apparatus[60] of Claim 1 wherein at least one of said microprotrusions[61] is a blade having a substantially rectangular cross-section in which the length of said rectangle is at least two times the cross-section of said rectangle.

5. The apparatus[60] of Claim 1 wherein said microprotrusions[61] comprise molded polymer or metal microprotrusions[61] .

6. A method for administering a chemical or drug to a patient comprising the steps of: disrupting a layer of skin on said patient's body utilizing an apparatus[60] that disrupts the said layer without disrupting the underlying layers of skin; and applying said drug to said area of said patient's body.

7. The method of Claim 6 wherein said apparatus[60] comprises: cutting means comprising a plurality of microprotrusions[61] having a height less than or equal to said

thickness of said layer of skin; and stop means for preventing said apparatus[60] from penetrating said layer of skin beyond a predetermined distance.

8. The method of Claim 7 wherein said microprotrusions[61] comprise first and second groups of microprotrusions[61] extending from a substrate and wherein said stop means comprises a region of said substrate separating said first and second groups, said substrate region having a coefficient of friction less than said first and second groups of microprotrusions[61] .

9. The apparatus[60] of Claim 7 wherein said apparatus[60] further comprises means for moving said apparatus[60] relative to said layer of skin in a motion pattern parallel to said layer of skin.

FIGURE 1

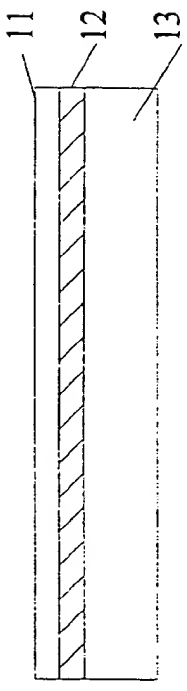


FIGURE 2

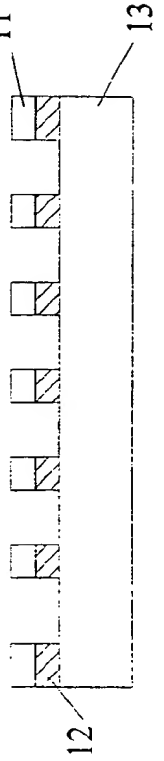


FIGURE 3

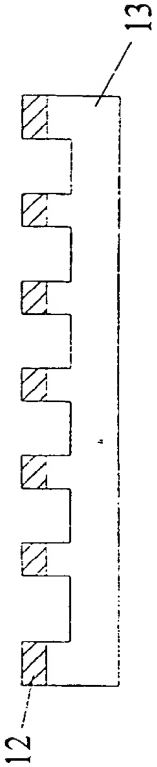


FIGURE 4

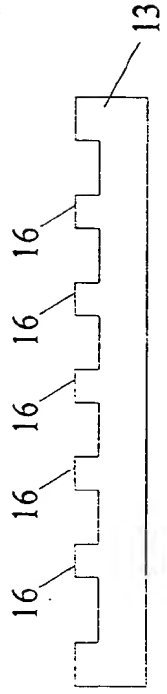
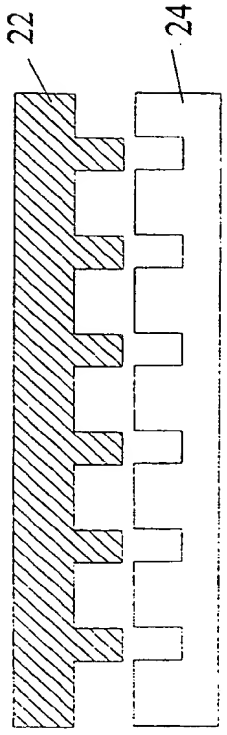


FIGURE 5



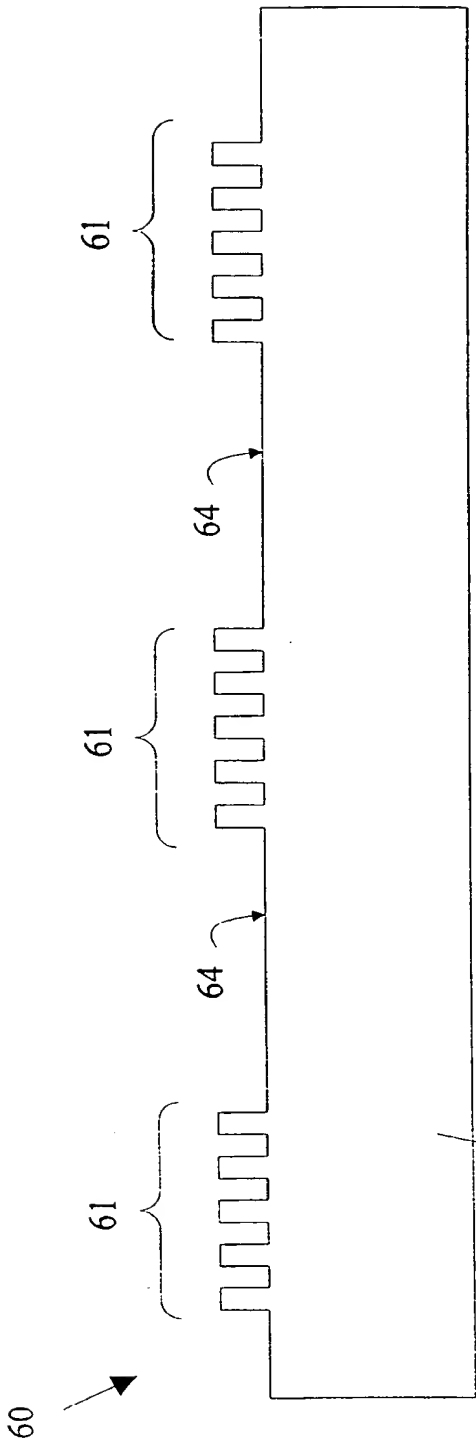


FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/06697

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 17/20
US CL :604/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/46-49, 51, 117, 181, 289, 290

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 3,675,766 (ROSENTHAL) 11 July 1972, note Fig. 1, and column 9 lines 7-16.	1-9
A	US, A, 4,711,247 (FISHMAN) 08 December 1987, note Fig. 1.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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